REMARKS

The Claimed Invention:

The claimed invention relates to methods for treating a vascular disorder that include a step of selecting an individual having an elevated level of a G-coupled Protease Activating Receptor (PAR)-1 and/or PAR-4. Specifically, the claimed invention uses increased levels of PAR-1 and/or PAR-4 as an indicator for statin administration. The cited references, alone or in combination, neither teach nor suggest the association between statins and PAR-1/PAR-4. Statins were known as a cholesterol lowering drug by inhibiting an HMG-CoA reductase. Therefore, prior to the claimed invention, the levels of total cholesterol, Low-Density Lipoprotein Cholesterol (LDL-C), and/or High-Density Lipoprotein Cholesterol (HDL-C) were assessed to determine if statins should be administered to individuals. The Applicant has discovered that statins inhibit PAR-1 and/or PAR-4 and that selecting individuals, based on their levels of PAR-1 and/or PAR-4 is a better indicator of statin administration. The claimed invention, based on this discovery, provides a new method of finding candidates, which expands the benefits beyond lipid profile modulation, for statin administration to treat a vascular disorder by assessing the levels of PAR-1 and/or PAR-4 regardless of levels of cholesterol.

Claim Objections

The Examiner objected Claims 1-2, 5-7 and 8 for improper periods within the sub-parts of certain claims. Applicant has amended the independent claims to remove the periods and replace them with ")". Applicant has amended Claim 10 to correct a typographical error. Therefore, the Applicant has obviated the rejection.

Claim Rejections - 35 U.S.C. §103

The Examiner rejected Claims 1-2, 5-14, and 22-23 under 35 U.S.C. §103(a) as being unpatentable over Whitney *et al* (U.S. 6,180,660 B1) (hereinafter Whitney) in view of Kahn *et al* (Journal of Clinical Investigation, Vol. 103, No.6, 1999) (hereinafter Kahn) and Gershlick *et al* (BMJ, Vol. 316, 1998) (hereinafter Gershlick).

The Examiner states that Whitney teaches methods for preventing or reducing the risk of a first occurrence of a cardiovascular event using an HMG-CoA reductase inhibitor alone or in combination with another lipid altering agent. The Examiner further states that Kahn teaches that platelet dependent arterial thrombosis underlies myocardial infarction and the researchers address the roles of PAR-1 and PAR-4 in activation of human platelets by thrombin. According to the Examiner, because of the role of thrombin and platelet activation in myocardial infarction and other pathological processes, identifying and blocking the receptors by which thrombin activates platelets has been an important goal. Furthermore, the Examiner states that Gershlick teaches that aspirin seems to be as beneficial as thrombolytic drugs and further that lifelong treatment with aspirin after myocardial infarction seems to be generally accepted. In addition, the Examiner states that aspirin affects the arachidonic acid pathway which activates platelet formation. According to the Examiner, one of ordinary skill in the art would have been motivated to select patients with elevated PAR-1 and PAR-4 levels because the activated PAR-1 and PAR-4 activate thrombin which activated platelets which, in turn, is the underlying cause of myocardial infarction.

The Applicant respectfully disagrees. The claimed invention provides new methods of selecting individuals for statin administration to treat a vascular disorder, regardless of cholesterol levels. Specifically, based on the discovery that statins inhibit PAR-1 and/or PAR-4, the increased levels of PAR-1 and/or PAR-4 can be used as a new indicator for statin administration. In other words, to determine if statins should be administered, physicians assess the levels of PAR-1 and/or PAR-4 instead of cholesterol levels.

In particular, Whitney discloses the effect of statins to treat myocardial infarction by inhibiting HMG-CoA reductase and teaches the assessment of cholesterol levels for statin administration (column 4, line 65 through column 5, line 14). However, there is no evidence in the cited references that teach and/or suggest the effect of statins on PAR-1 and/or PAR-4. Selective PAR-1/PAR-4 inhibition by statins is an entirely different pathway than what Whitney teaches, and was clearly unknown at the time of filing. The cited references do not at all consider PAR-1/PAR-4 inhibition by statins, and accordingly selection of individuals based on their PAR-1/PAR-4 levels is even not mentioned, and certainly not suggested by the cited art. The PAR-1/PAR4 inhibition represents an entirely distinct and unique property of statins,

representing a piece of potential "statin pleiotropy" clearly not covered by the technology disclosed in Whitney.

Furthermore, it was previously unknown how this outcome benefit is achieved. For example, is the outcome related to lipid modulation, or PAR-1/PAR-4 inhibition, or does it represent a cumulative effect? The claimed invention and the data in the specification surprisingly and strongly support the different mechanisms beyond lipid modulation and in particular, PAR-1/PAR-4 blockade by which statins exert their activity. This mechanism of action directly affects how individuals are selected, and selecting patients based on their PAR-1/PAR-4 level is an important step in the claimed invention. As such, selection of PAR-1/PAR-4 patients is clearly not suggested or obvious in light of the cited references. Therefore, one having ordinary skill in the art could not have contemplated the step of assessing levels of PAR-1 and/or PAR-4 as an indicator for statins administration, as claimed in the invention.

According to the Examiner, Kahn discloses roles of PAR-1 and PAR-4 in activation of human platelets by thrombin. However, Kahn does not suggest the effect of statins on PAR-1/PAR-4. Kahn is simply providing an early basic review on PAR-1/PAR-4 receptors, and thrombin-induced platelet activation. However, statins are not mentioned at all in the Kahn paper. The fact that statins affect PAR-1/PAR-4 platelet receptors are not acknowledged nor discussed in this cited reference. It is unclear to the Applicant how one of skill in the art would have combined Whitney with Kahn when Whitney makes no mention of PAR-1/PAR-4 and Khan makes no mention at all of statins. Even taken together, one of skill in the art would not have been motivated to combine the references since the PAR-1/PAR-4 mechanism or effect on statins was not known, nor suggested. The selection of patients having an elevated level of PAR-1 and/or PAR-4, and to assess the need for statin administration was never contemplated by a skilled artisan even in light of the cited references.

Furthermore, the Examiner states that Gershlick discloses the effect of aspirin on myocardial infarction as compared to a thrombolytic drug. However, it is irrelevant to the claimed invention. Aspirin involves entirely different mechanisms of action, and entirely different targets within the platelet receptors. To extrapolate the aspirin data to potential effects of PAR-1/PAR-4 inhibitors is scientifically invalid. Gershlick does not mention statins nor any

PAR-1/PAR-4 association thereto. Accordingly, Applicant submits that Gershlick does not provide any impact on the patentability of the claimed invention.

Taken together, the cited references, alone or in combination, neither teach nor suggest the relationship between statins and platelet PAR-1/PAR-4. Therefore, one having ordinary skill in the art could not have been motivated to assess the levels of PAR-1 and PAR-4 for statin administration from the cited references at the time of invention. Although the Supreme Court in KSR cautioned against an overly rigid application of teaching-suggestion-motivation (TSM) test, it also recognized that TSM was one of a number of valid rationales that could be used to determine obviousness. *KSR International Co. v. Teleflex Inc.* (KSR), 82 USPQ2d 1385, 1396 (2007) (citing *In re Bergel*, 292 F.2d 955, 956-57, 130 USPQ 206, 207-208 (1961)). The Examiner states that one of ordinary skill in the art would have been motivated to select patients with elevated PAR-l and PAR-4 levels because it is well known that PAR-1 and PAR-4 activate thrombin which activates platelets which, in turn, is the underlying cause of myocardial infarctions.

The Applicant strongly and respectfully disagrees. The step of assessing levels of PAR-1 and/or PAR-4 in the claimed invention is used to determine if statins should be administered. That is, the levels of PAR-1 and/or PAR-4 is assessed not to select an individual having myocardial infarction, but to select an individual who needs statin administration. Therefore, the claimed invention provides new methods for treating a vascular disorder including the step of selecting individuals having increased levels of PAR-1 and/or PAR-4 and thus makes it possible for physicians to use the increased levels of PAR-1 and/or PAR-4 as a new indicator for statin administration instead of cholesterol levels. As described herein, none of the cited references, alone or in combination teach or suggest the relationship between stains and platelet PAR-1/PAR-4. Without the discovery by the Applicant that statins inhibit PAR-1 and/or PAR-4, one having ordinary skill in the art could not have contemplated or been motivated to use the increased levels of PAR-1 and/or PAR-4 as an indicator for statin administration. Specifically, combining Whitney, which described the effect of statins to treat myocardial infarction by inhibiting HMG-CoA reductase, with Kahn, which describes the roles of PAR-1 and PAR-4 in activation of human platelets, and Gershlick, which describes aspirin administration, do not amount to the claimed invention, namely, selecting an individual having increased levels of PAR-1 and/or PAR-4 for statin administration. According to the cited references, there was no evidence nor knowledge at the time of filing that statins provide their benefit by PAR-1/PAR-4

platelet inhibition, and therefore selection of PAR-1/PAR-4 patients as an indicator for statin administration was clearly unknown and not contemplated by a skilled artisan. Therefore, the claimed invention is not obvious to one having ordinary skill in the art at the time the invention made.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner does not agree that the claims are in conditions for allowance, the examiner is *encouraged* to call the undersigned for an interview to discuss any remaining issues.

Respectfully submitted,

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